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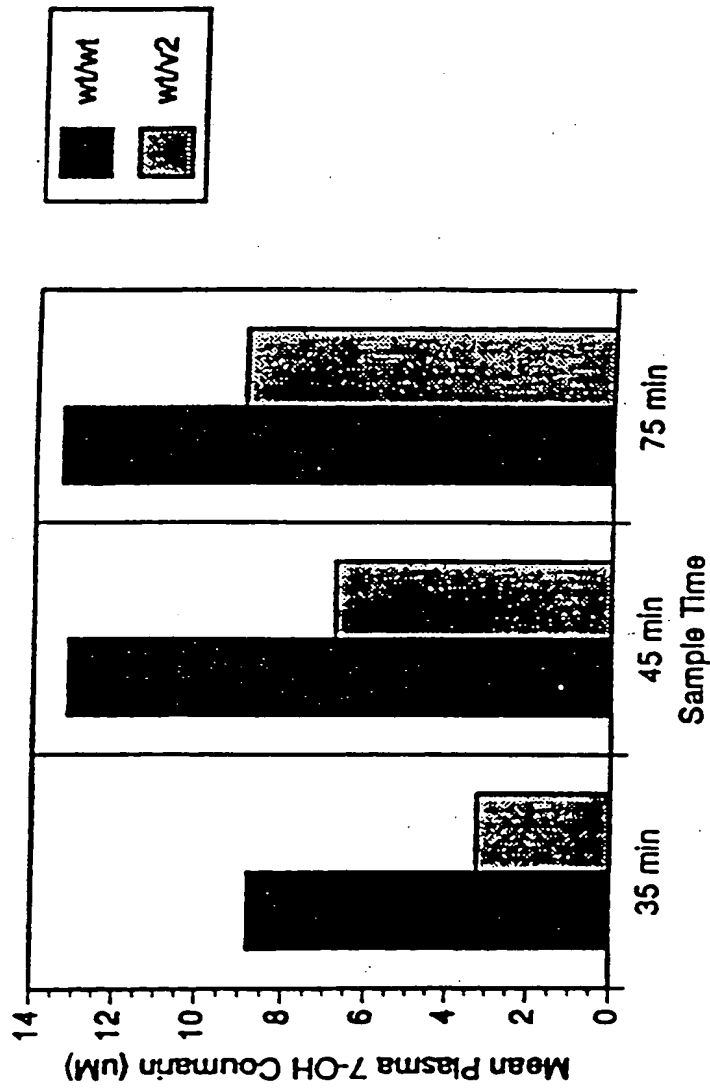
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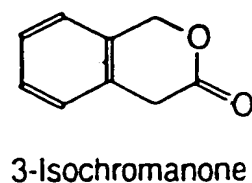
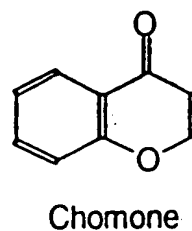
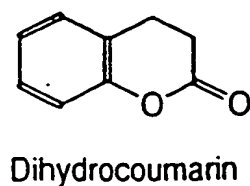
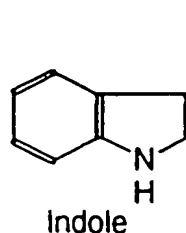
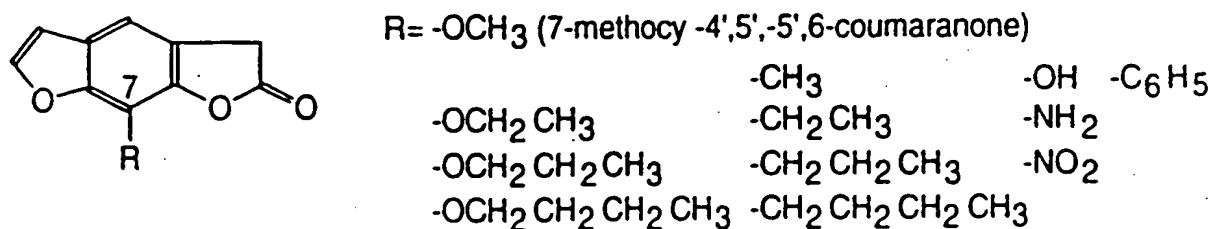
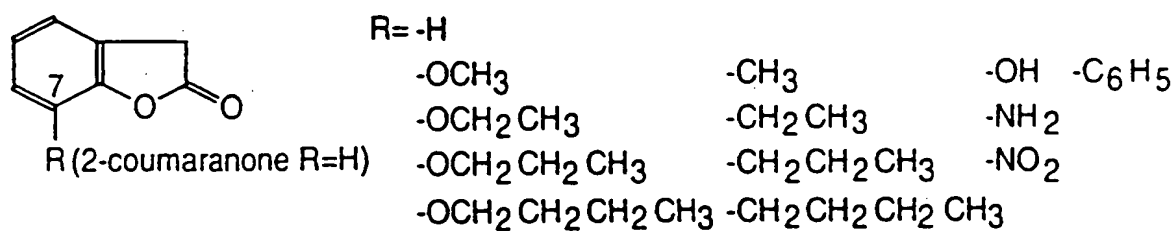
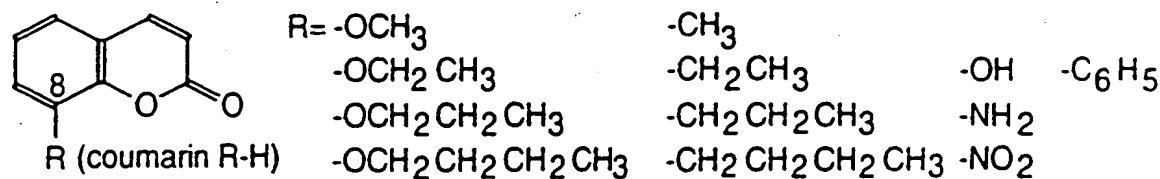
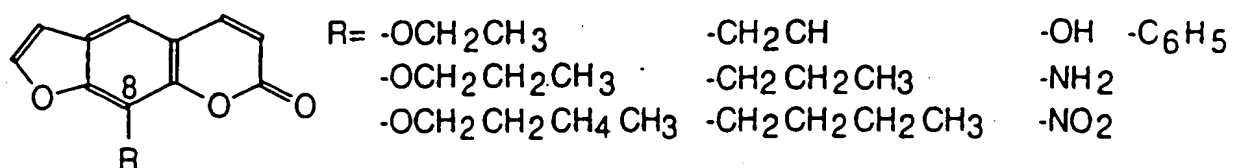
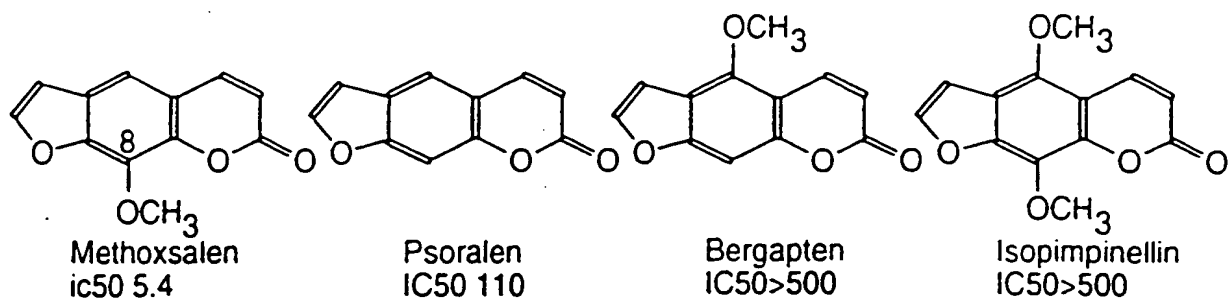
FIGURE 1

Heterozygous CYP2A6 individuals have lower CYP2A6 activity than wild type/wild type (wt) individuals

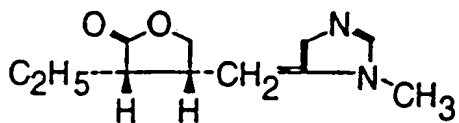


Application of a method to characterize CYP2A6 activity in human subjects by taking plasma samples at times as early as 35 minutes after administration of an oral dose of coumarin (100 mg in this example). Lower doses of coumarin may also be used and the data can also be expressed as a ratio of coumarin/7-OH coumarin. The test can also be performed using oral nicotine or another CYP2A6 substrate.

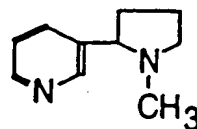
2/23
FIGURE 2A



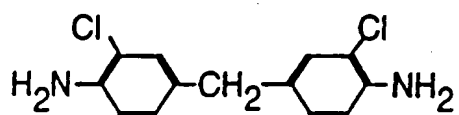
3/23
FIGURE 2B



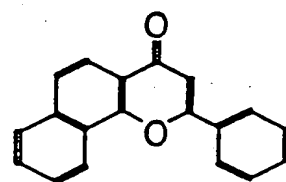
Pilocarpine



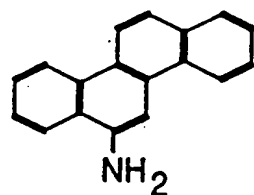
Nicotine



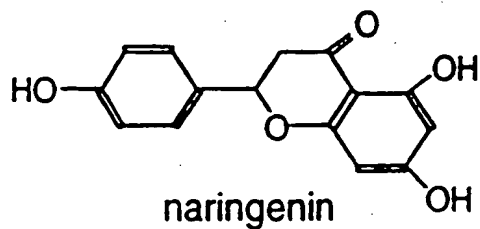
4,4'-Methylene bis[2-chloroaniline]



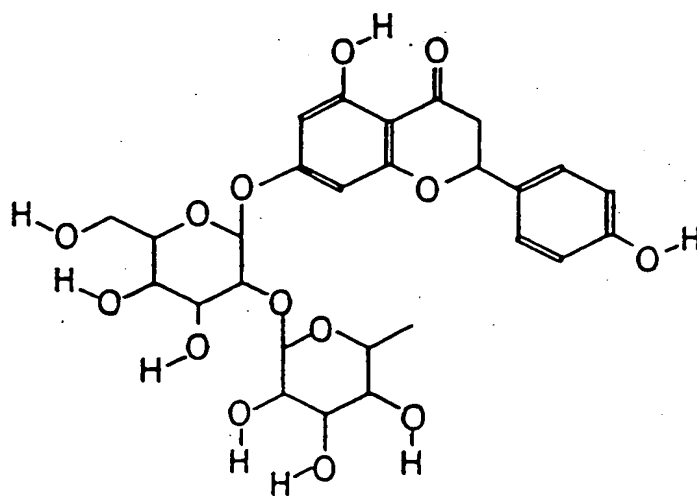
6-Aminochrysene



α-Naphthoflavone

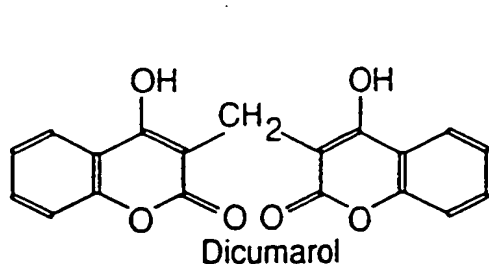


naringenin

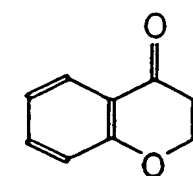


naringin

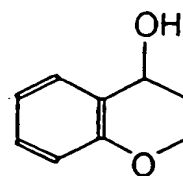
4/23
FIGURE 2C



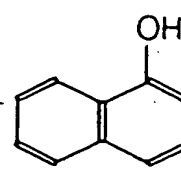
About 80% activity left at 0.05 mM concentration



4-Chromanone

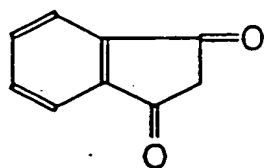


4-Chromanol

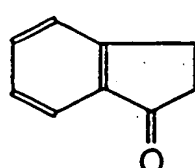


1-Naphthol

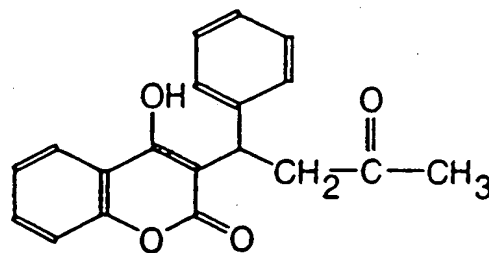
70% inhibition at
 0.5 mM concentration



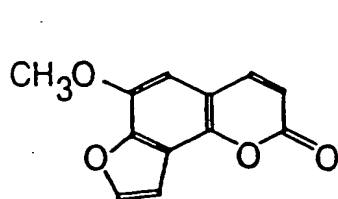
1,3-Indandione



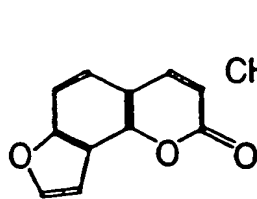
1-Indanone



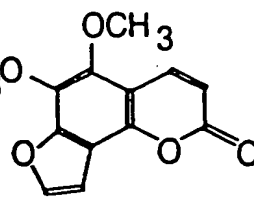
Warfarin



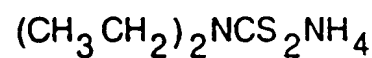
Sphondin
 IC50 90



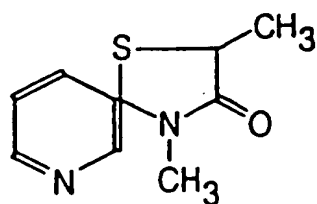
Amgelicin
 IC 50 160



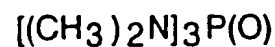
Pimpinlin
 IC50>500



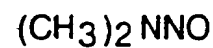
Diethyldithiocarbamic acid
 ammonium salt



SM-12502



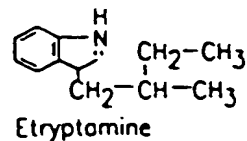
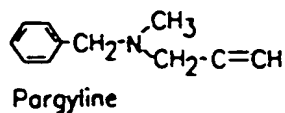
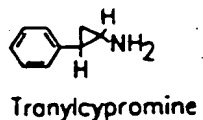
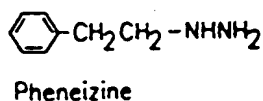
Hexamethylphosphoramide



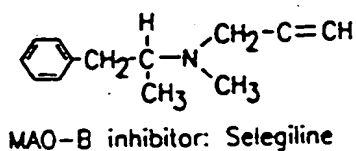
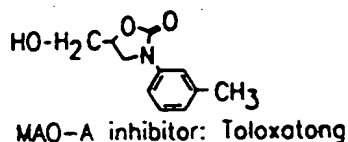
N-Nitrosodimethylamine

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FIGURE 2D

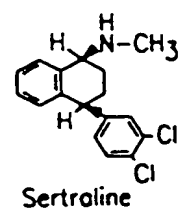
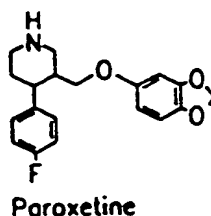
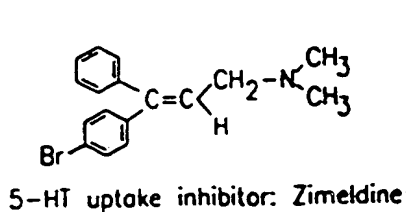
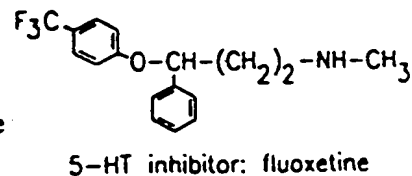
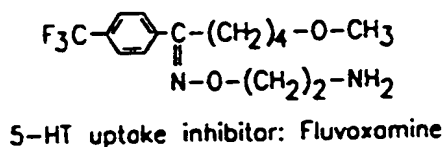
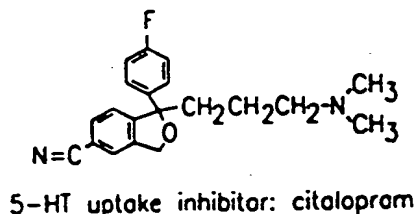
Non-selective MAO inhibitors



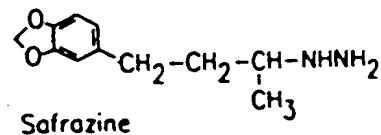
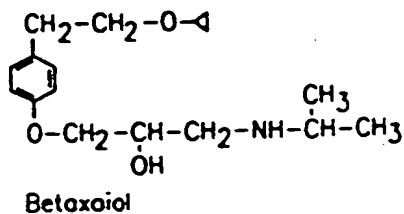
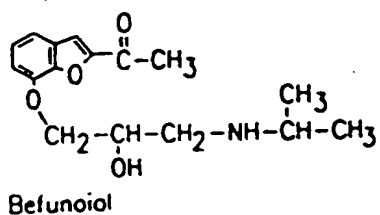
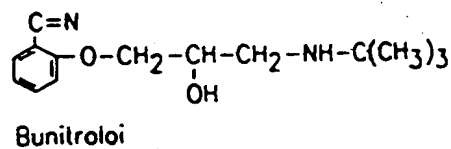
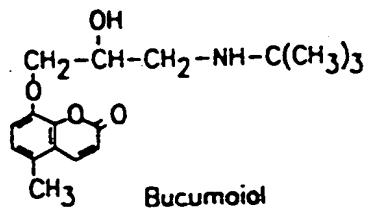
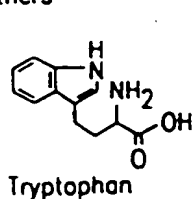
Selective MAO Inhibitors



Antidepressants

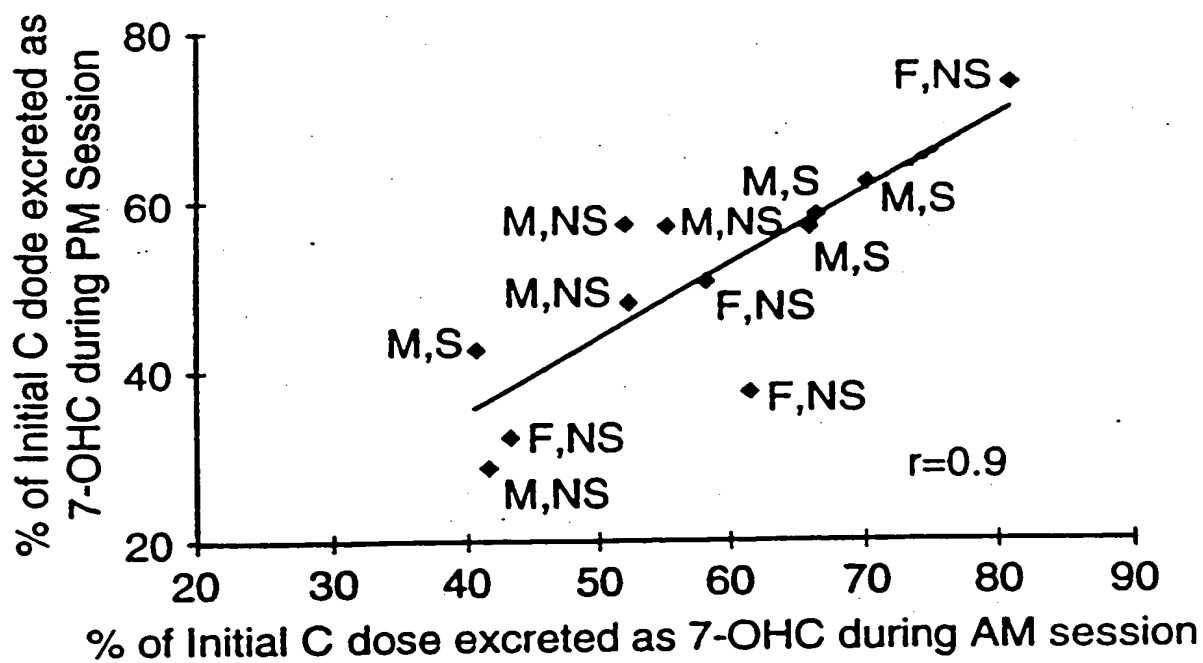


Others

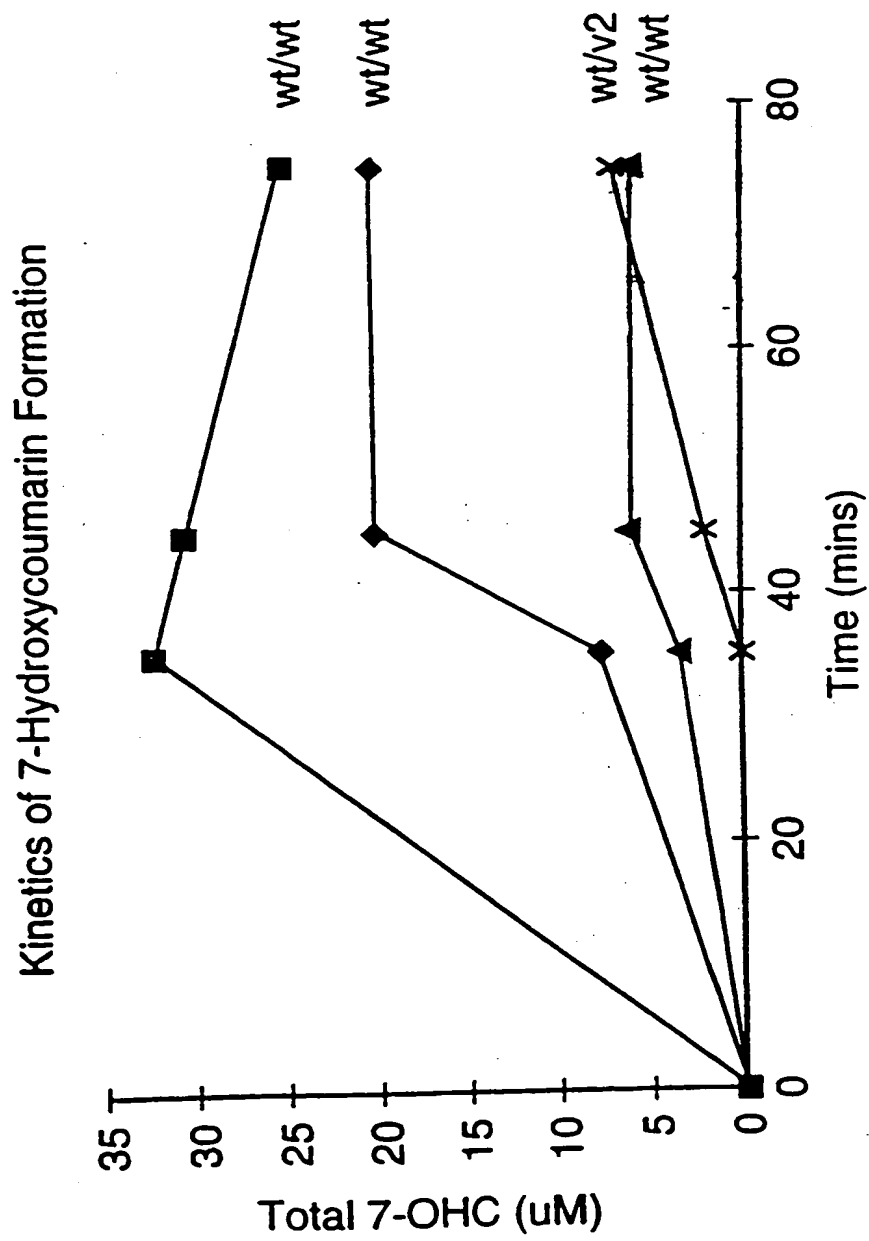


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FIGURE 3

Comparision Between Morning and Afternoon Testing Sessions.



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FIGURE 4



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FIGURE 5

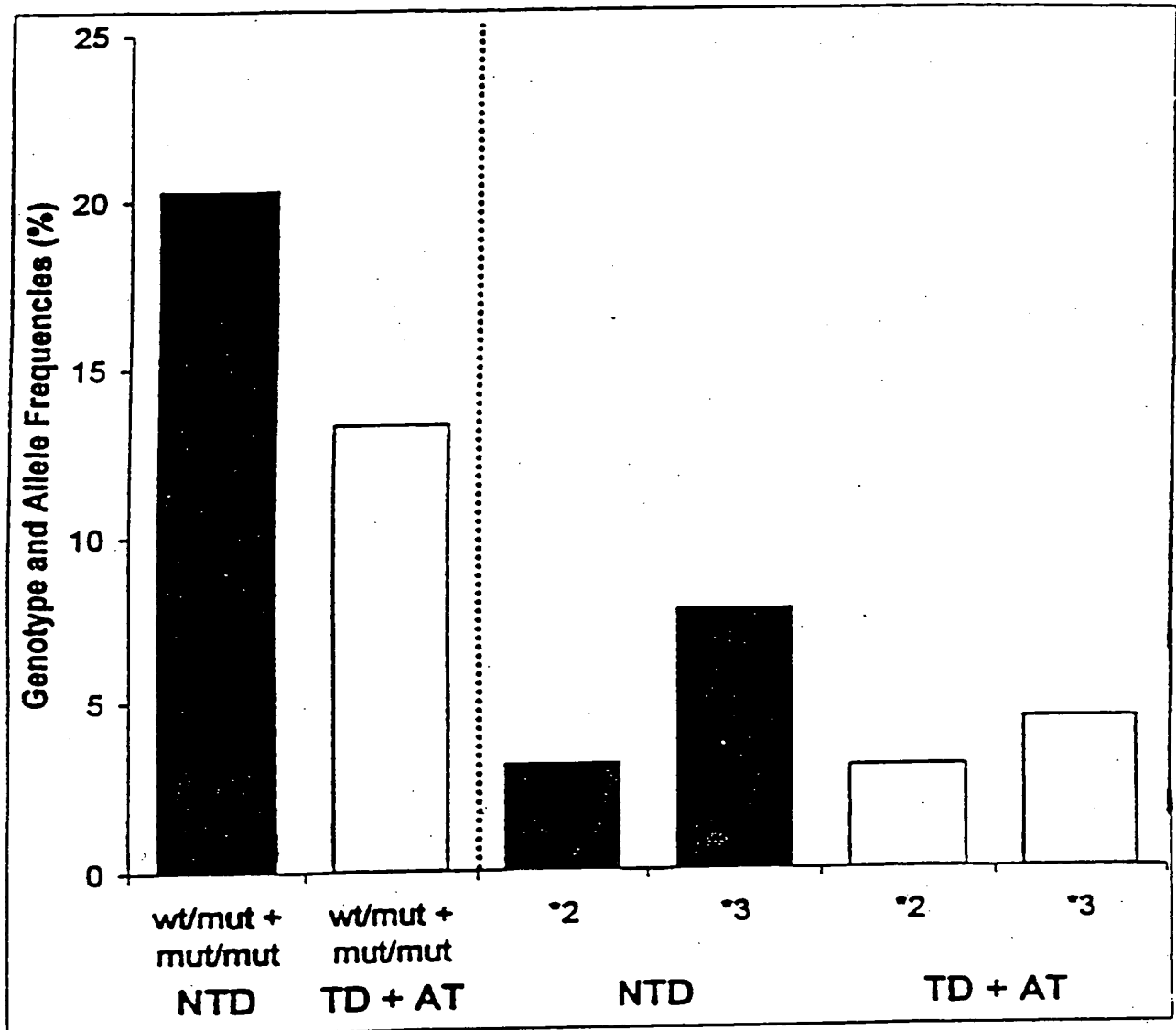
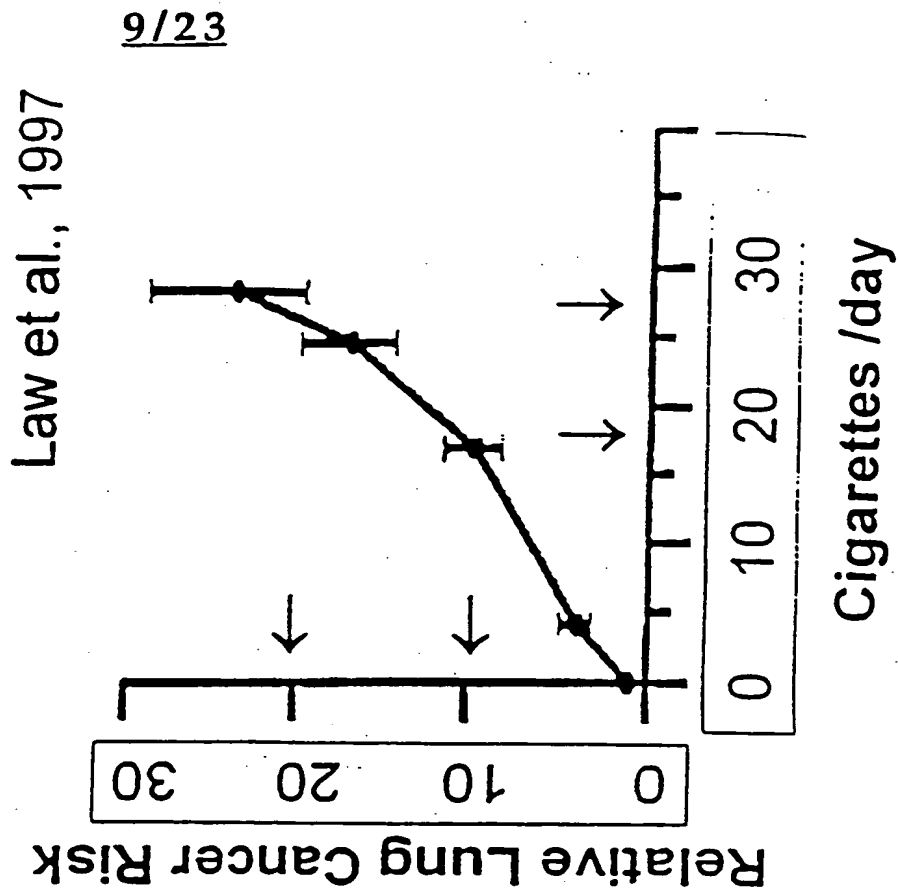
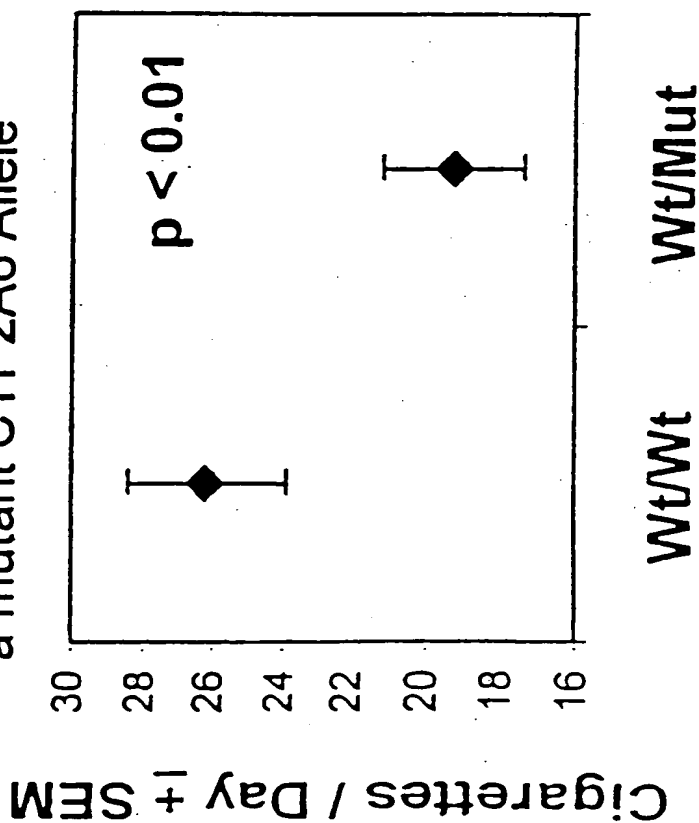


FIGURE 6

Tobacco Used by Smokers
without (wt/wt) or with (wt/mut)
a mutant CYP2A6 Allele



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FIGURE 7

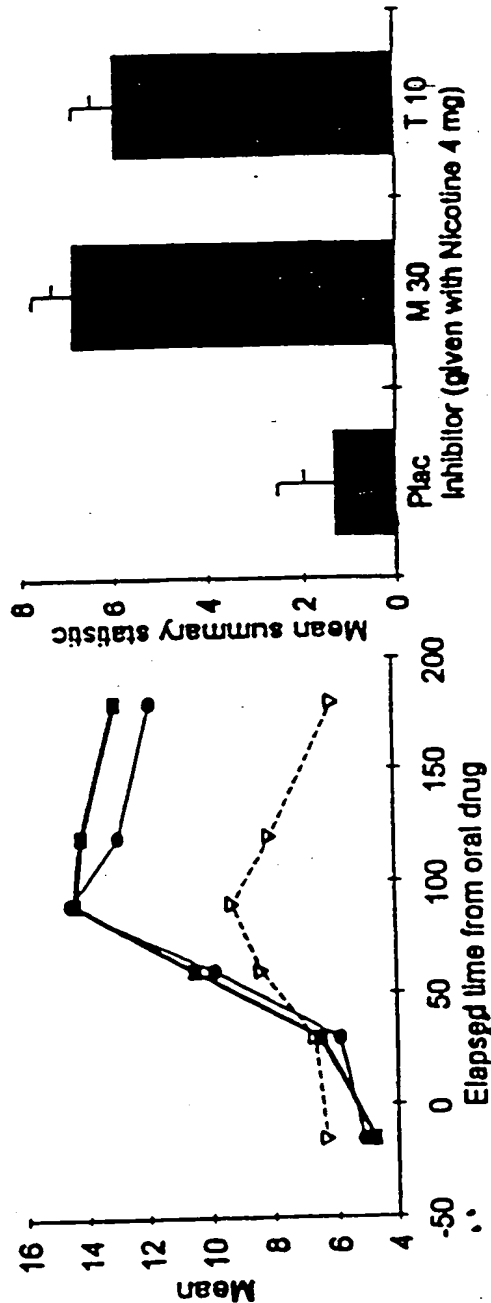
Plasma nicotine, ng/ml

Comparison	F	p	Significant drug-vs-drug differences
Main effect of drug	21.830	0.000	M 30
Main effect of sex	1.480	0.252	Plac
Drug*sex interaction	1.250	0.309	M 30
			T 10

0.0001

0.0001

Post-drug mean minus baseline



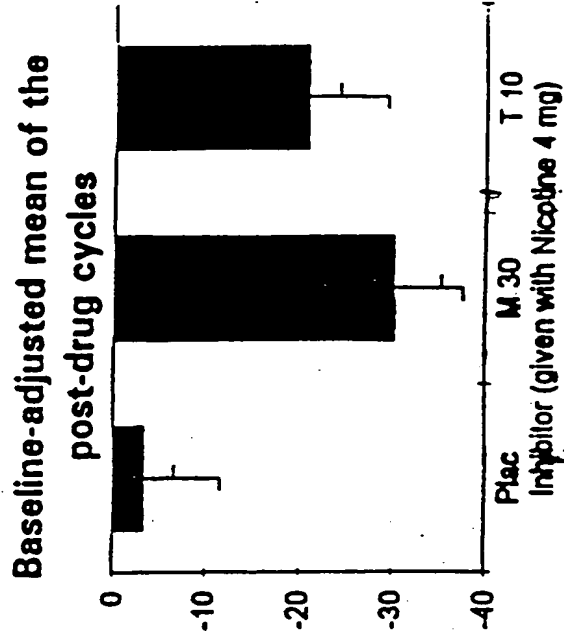
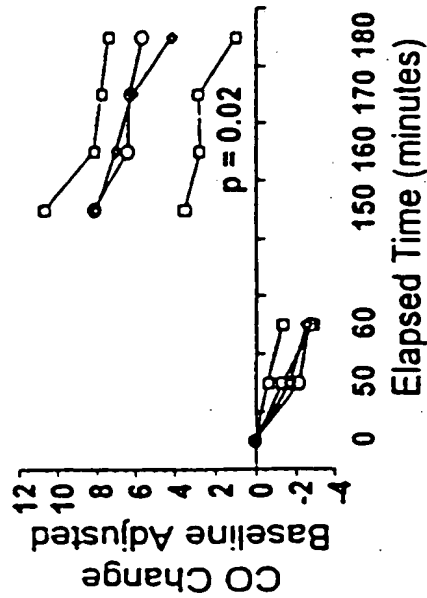
Means are shown with standard errors

FIGURE 8

Current desire to smoke

Comparison	F	P	Significant drug-vs-drug differences	
Main effect of drug	8.220	0.003 **	M 30	T 10
Main effect of sex	2.180	0.170	Plac	
Drug*sex interaction	3.390	0.054	M 30	0.0171
			T 10	

Baseline-adjusted mean of the post-drug cycles



Means are shown with standard errors

FIGURE 9

Carbon monoxide, parts/million

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.880	0.022 *				
Main effect of sex	0.380	0.554				
Drug*sex interaction	1.370	0.277				
Meth/Nic vs others	11.380	0.003 **	Meth/Nic	0.0078	0.0082	0.0204
			Meth/Plac			
Among others	0.100	0.904	Plac/Nic			

Increase during smoking

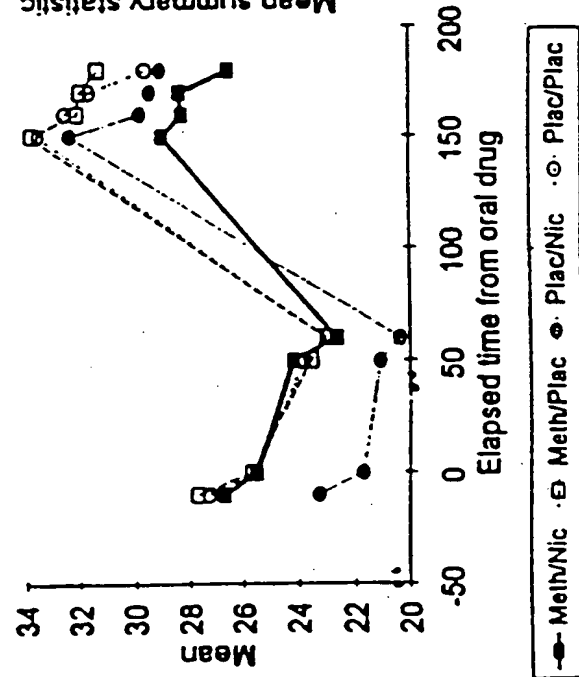
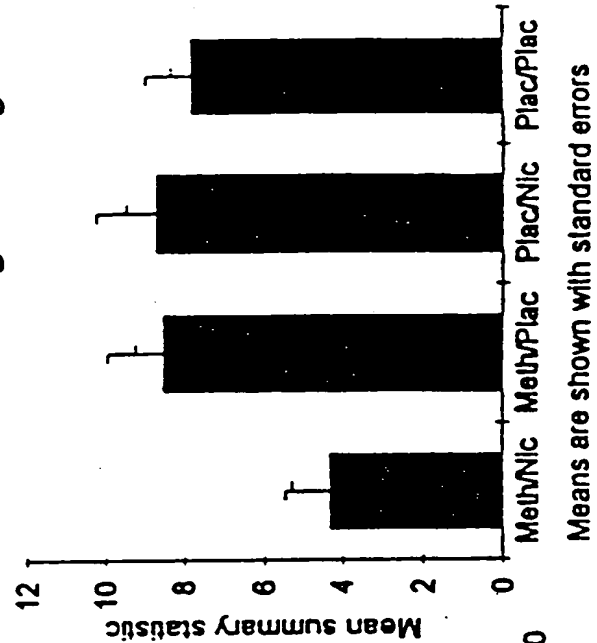


FIGURE 10

Ratio of plasma nicotine increase to CO increase during smoking

Comparison	F	p	Significant drug-vs-drug differences		
Main effect of drug	5.810	0.004 **	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	1.620	0.235	Meth/Nic	0.0039	0.0061 0.0008
Drug*sex interaction	0.800	0.506	Meth/Plac		
			Plac/Nic		
Meth/Nic vs others	16.720	0.000 **			
Among others	0.380	0.689			

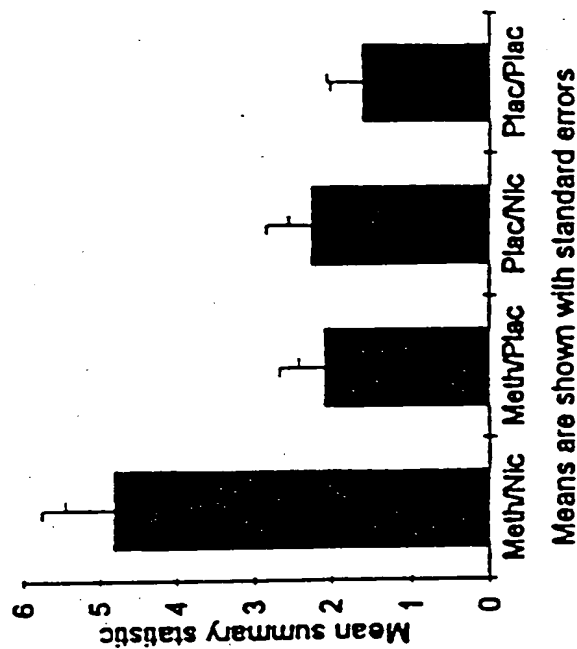


FIGURE 11

Number of cigarettes smoked

Comparison	F	p	Significant drug-vs-drug differences			
Main effect of drug	3.670	0.026 *	Meth/Nic	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	0.470	0.509				
Drug*sex interaction	1.490	0.243				
Meth/Nic vs others	7.510	0.011 *				
Among others	1.860	0.177				

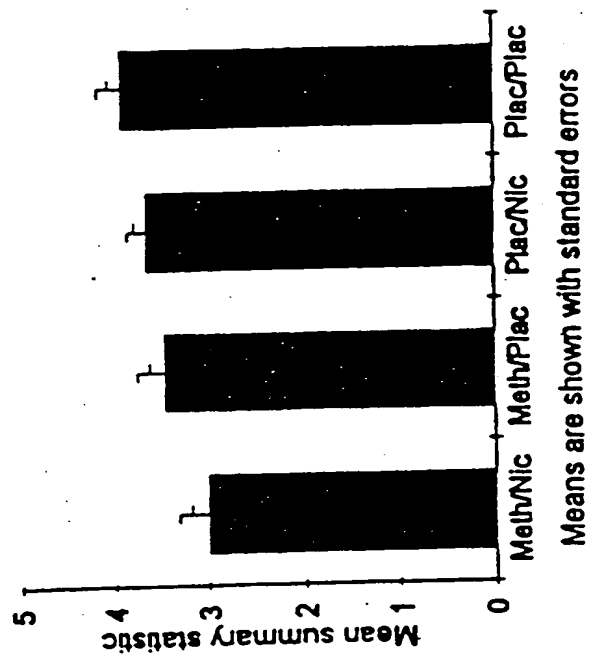


FIGURE 12

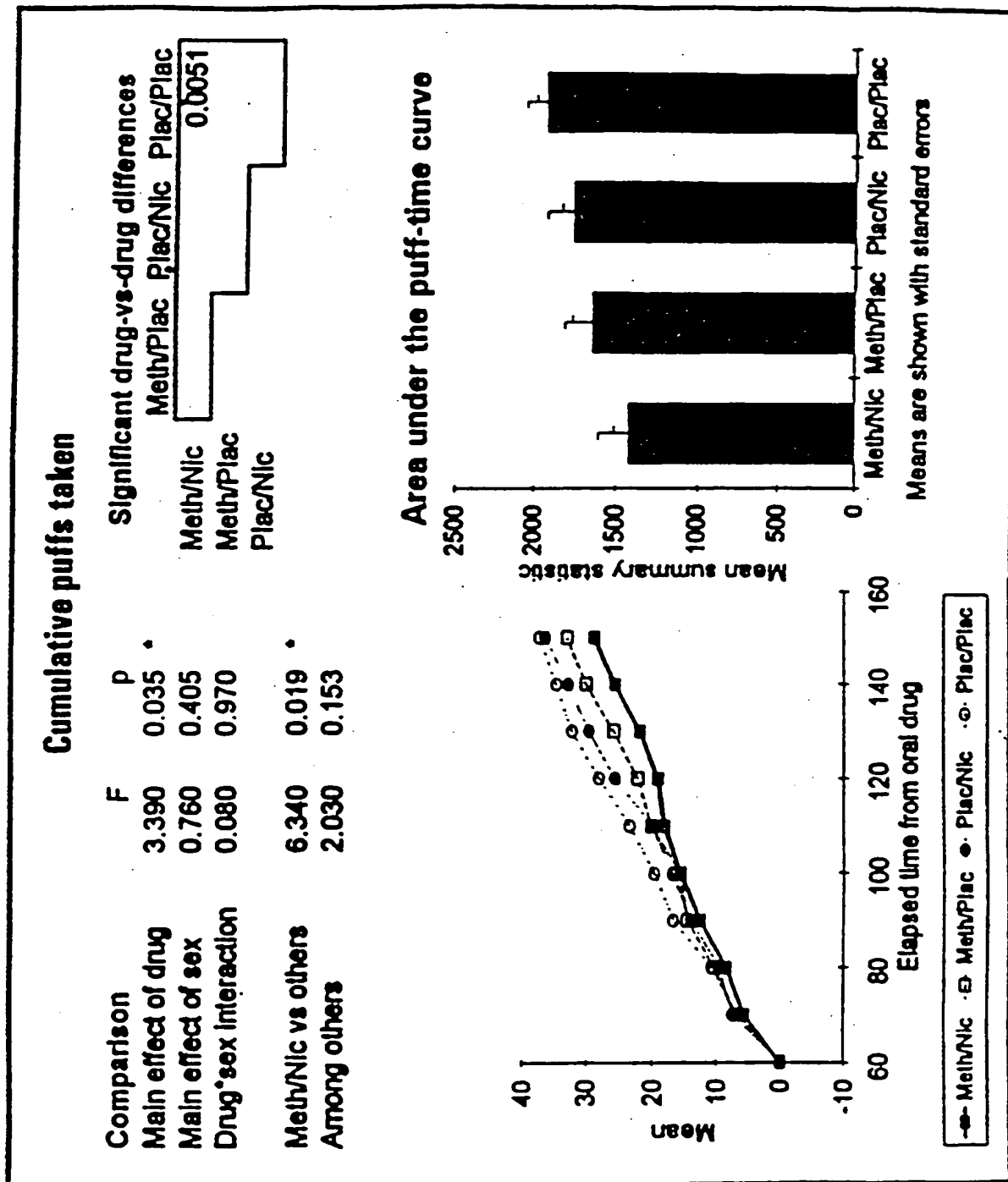


FIGURE 13

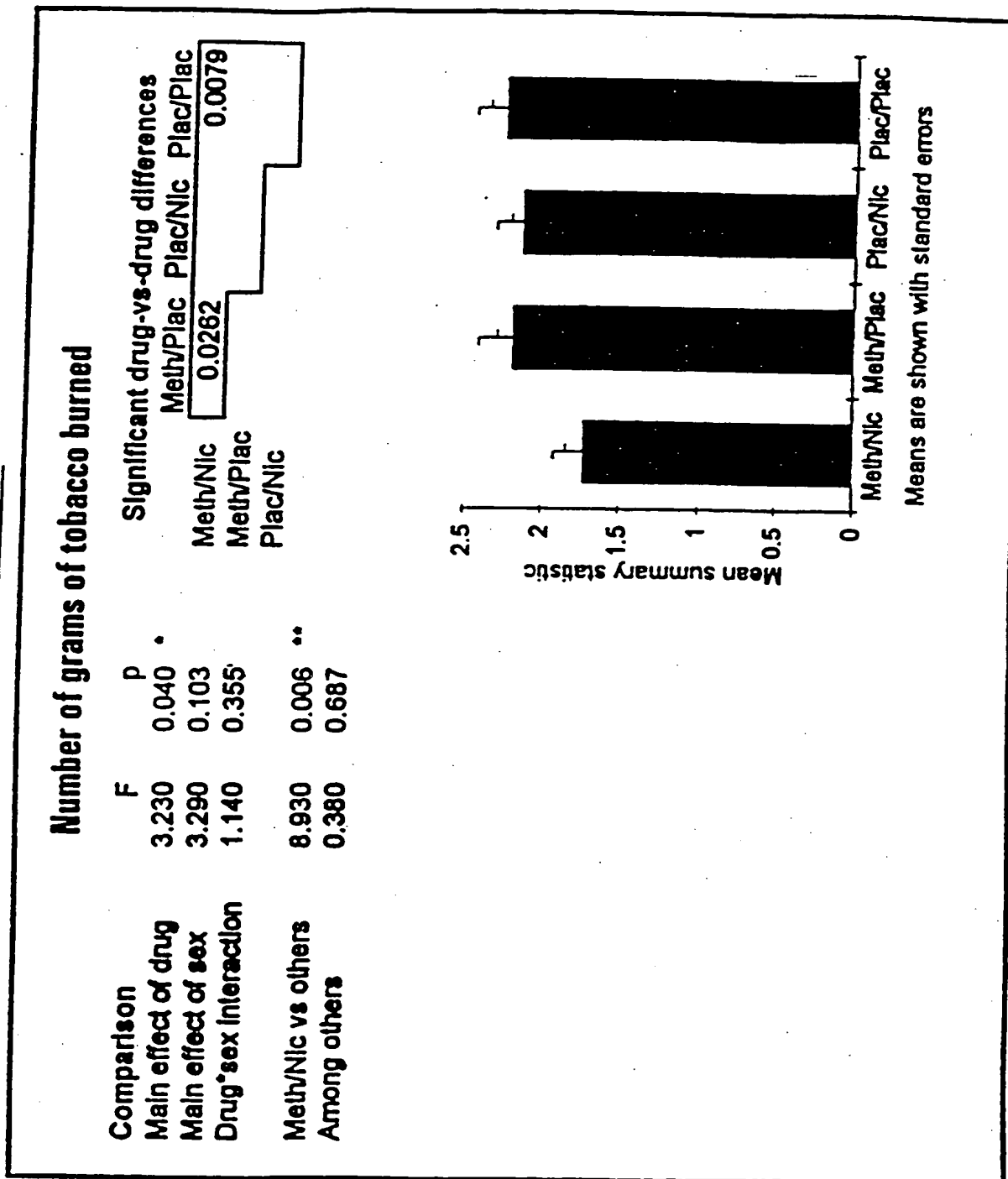


FIGURE 14

Latency between first two cigarettes, minutes

Comparison	F	p	Significant drug-vs-drug differences		
Main effect of drug	2.820	0.060	Meth/Plac	Plac/Nic	Plac/Plac
Main effect of sex	0.810	0.392			
Drug*sex interaction	0.170	0.914	Meth/Nic		0.0097
			Meth/Plac		0.047
			Plac/Nic		
Meth/Nic vs others	3.950	0.059			
Among others	2.350	0.117			

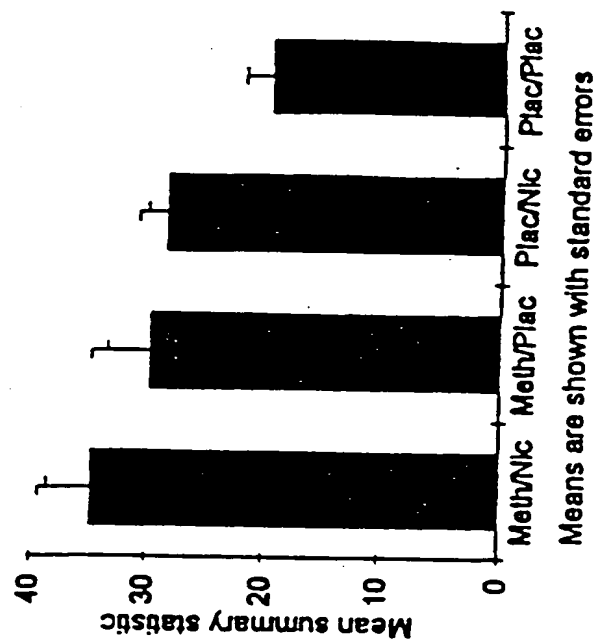
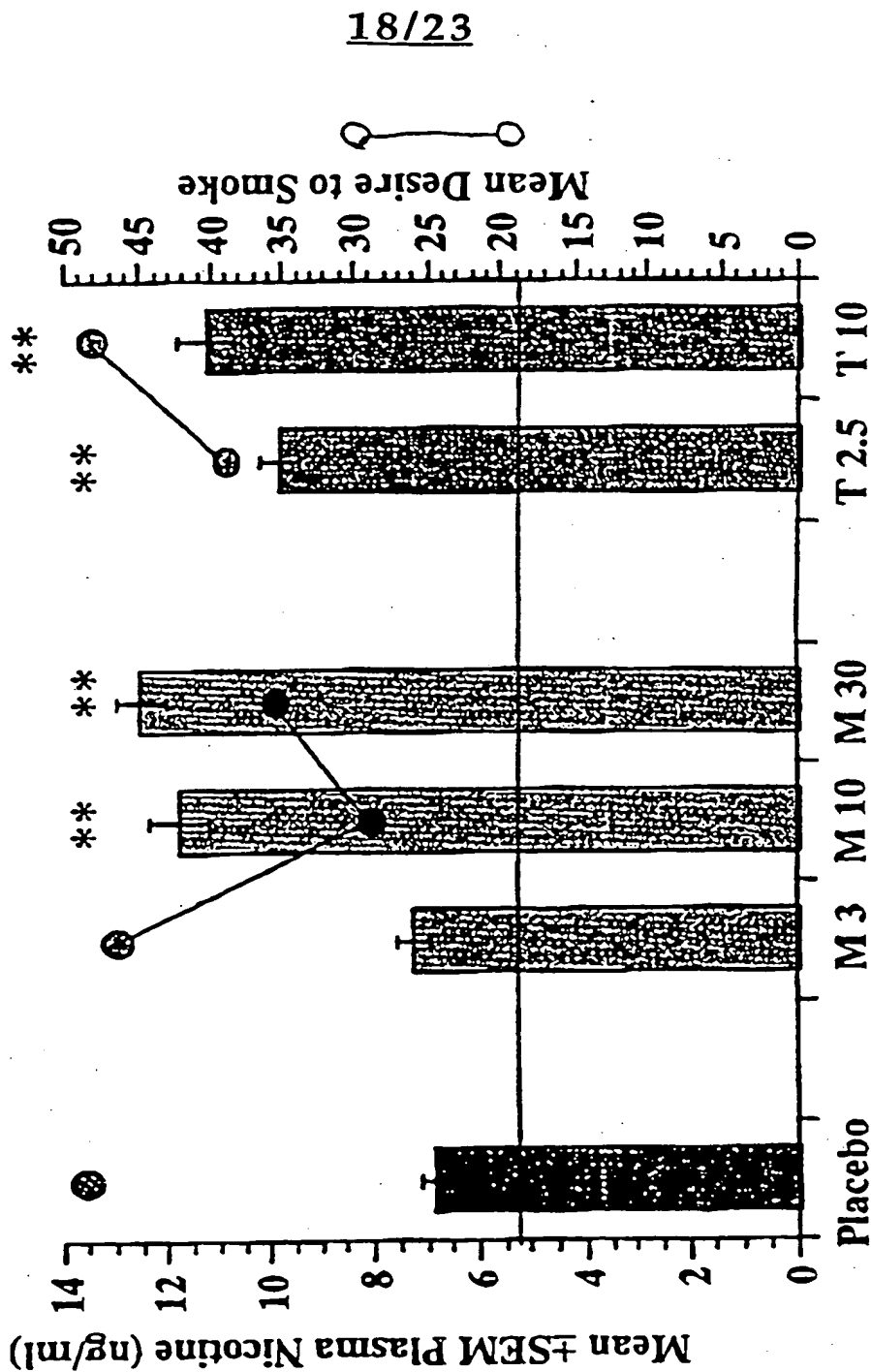


FIGURE 15

Methoxsalen and Tranlycypromine Increase Oral Nicotine Bioavailability and Decrease Desire to Smoke



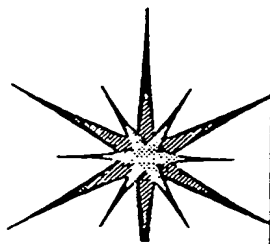


FIGURE 16

Extracts of St. John's Wort Inhibit Nicotine Metabolism in vitro

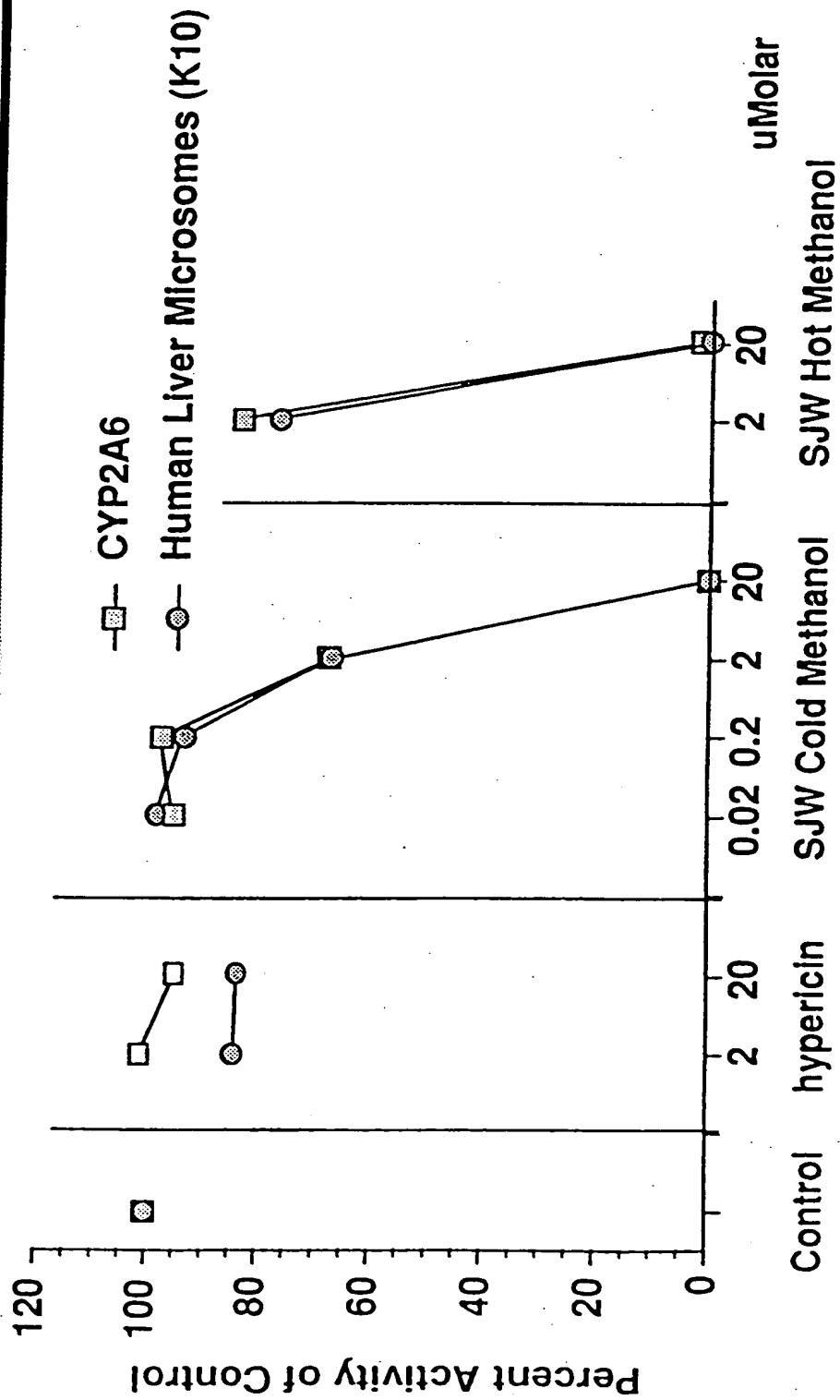


FIGURE 17

St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo

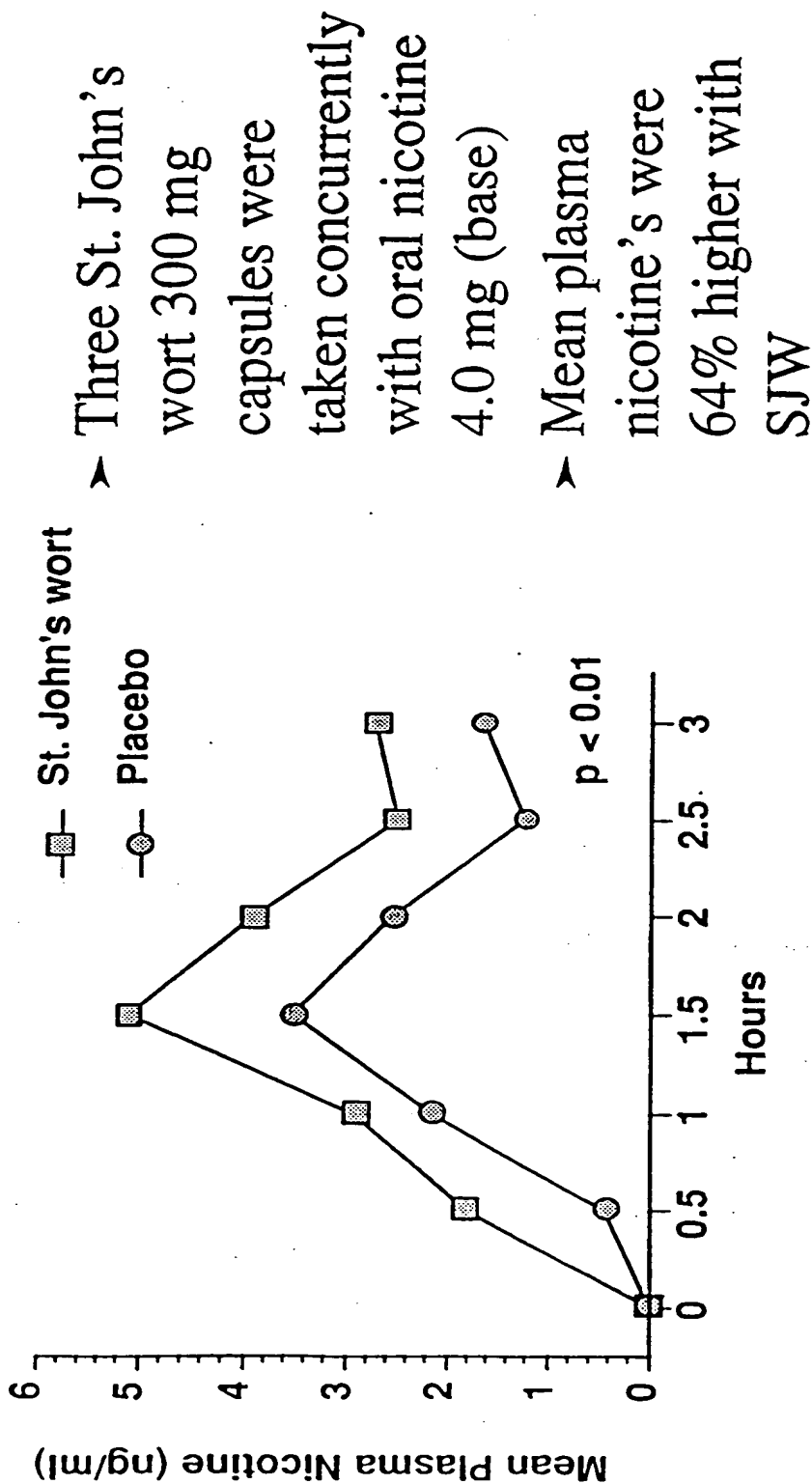
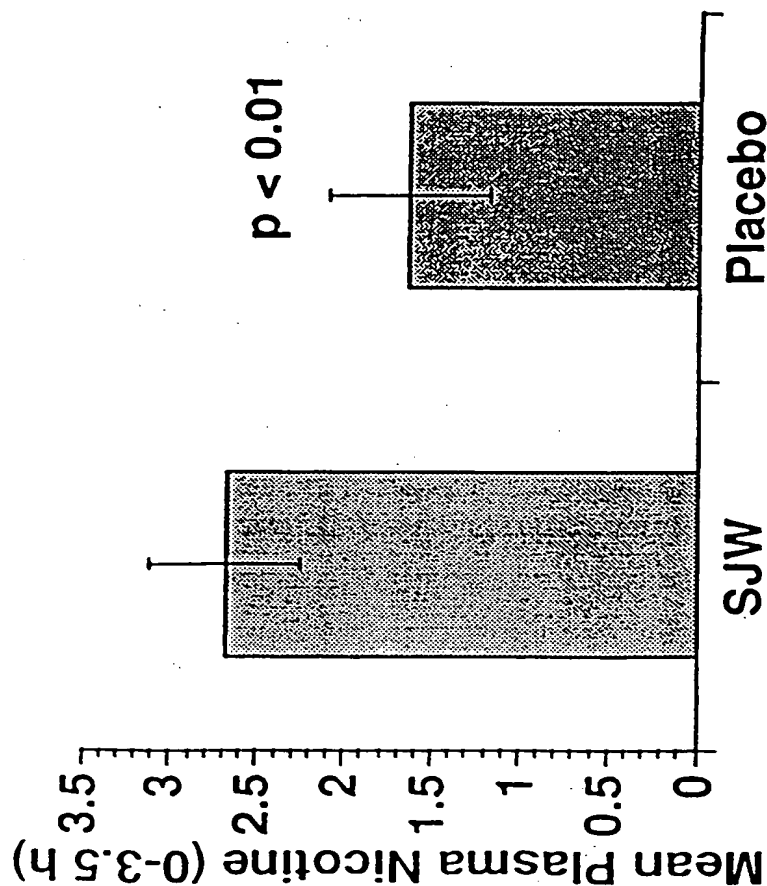


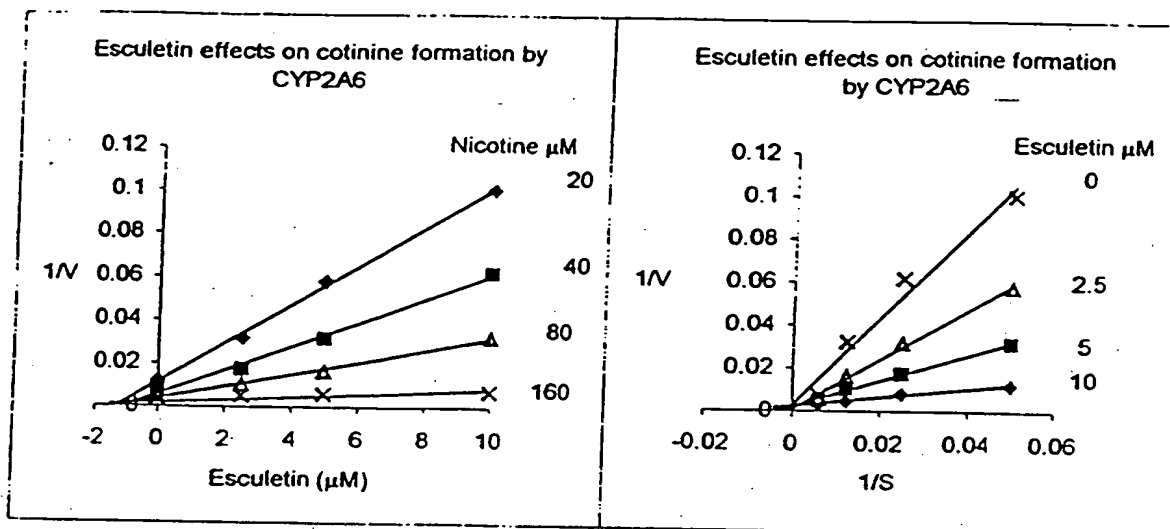
FIGURE 18

St. John's Wort (SJW) Increases Oral Nicotine Bioavailability in vivo

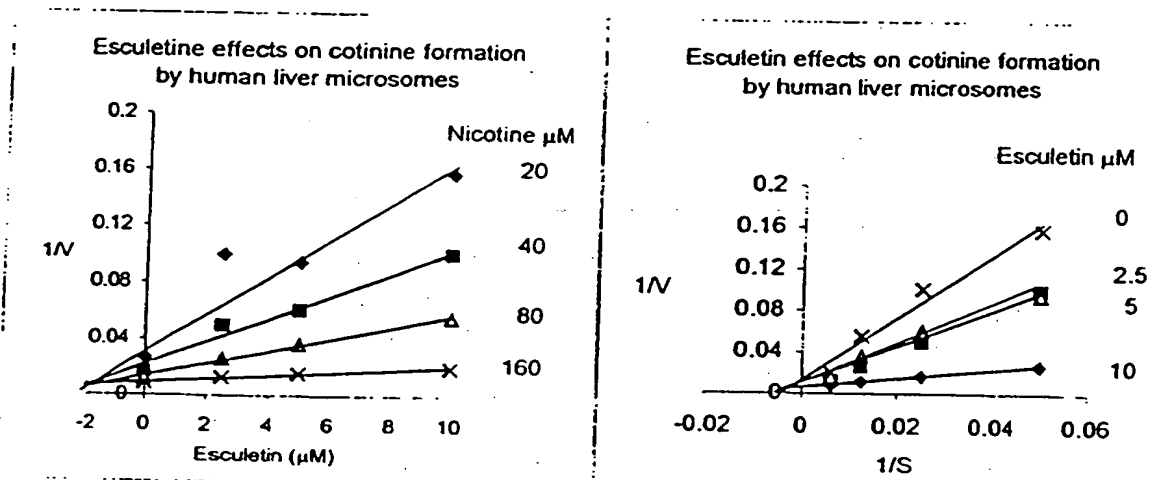


- > Three St. John's wort 300 mg capsules were taken concurrently with oral nicotine 4.0 mg (base)
- > Mean plasma nicotine's were 64% higher with SJW

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FIGURE 19

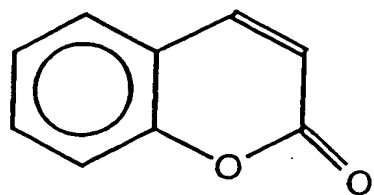


Estimated $K_i = 1 \mu\text{M}$
Calculated by PCS program $K_i = 1.1 \mu\text{M}$

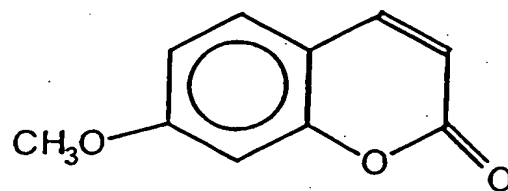


Estimated $K_i = 2 \mu\text{M}$
Calculated by PCS program $K_i = 1.6 \mu\text{M}$

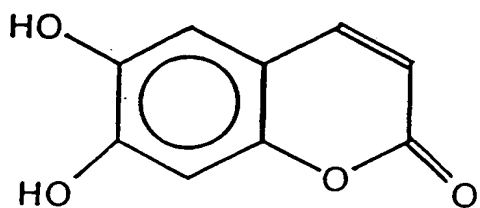
23/23
FIGURE 20



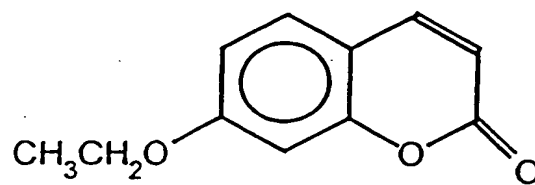
Coumarin



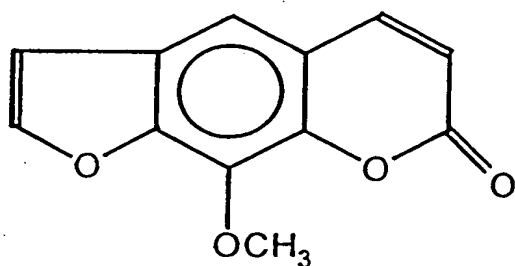
7-Methoxycoumarin



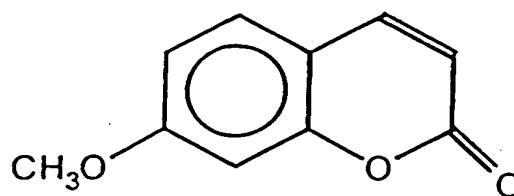
Esculetin



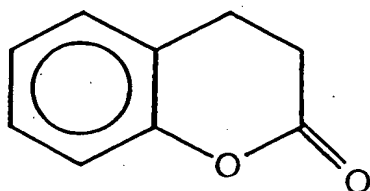
7-Ethoxycoumarin



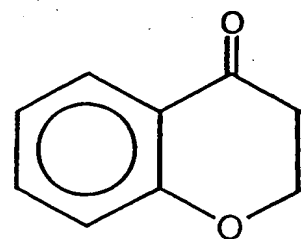
Methoxsalen



7-Methylcoumarin



Dihydrocoumarin



Chromone